A multicentre randomised open-label phase III study of stereotactic radiosurgery, in addition to standard systemic therapy for patients with metastatic melanoma or newly diagnosed metastatic NSCLC and asymptomatic or oligosymptomatic brain metastases.

Published: 23-05-2023
Last updated: 16-11-2024

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Metastases
Study type	Interventional

Summary

ID

NL-OMON53696

Source
ToetsingOnline

Brief title
19-21 USZ-STRIKE

Condition

- Metastases

Synonym
Brain metastatic melanoma, brain metastatic non-small cell lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: ETOP IBCSG Partners Foundation
Source(s) of monetary or material Support: Universitätsspital Zürich (USZ Foundation and its funding partners)

Intervention

Keyword: Brain metastases, Melanoma, Non small cell lung cancer, Stereotactic radiosurgery

Outcome measures

Primary outcome

CNS-specific PFS, locally assessed as per iRANO criteria.

Secondary outcome

- CNS-specific PFS per tumour cohort, locally assessed as per iRANO criteria

- CNS-specific PFS, overall and per tumour cohort, centrally assessed as per

iRANO

criteria

- Objective CNS-response rate, centrally assessed as per iRANO criteria

- Duration of CNS-response

- Pattern of CNS-specific progression (local versus distant progression)

- Extra-CNS progression, locally assessed as per RECIST v1.1

- Incidence of radio-necrosis and pseudo-progression in the CNS

- OS, overall and per tumour cohort

- Neurocognitive function

- Quality of life and functional independence

- Toxicity by CTCAE v5

Study description

Background summary

Central nervous system (CNS) metastases are a growing challenge in oncology, due to
increasingly effective therapies at non-CNS sites and thus overall longer survival. Brain
metastases may affect up to 30% of patients with metastatic cancer and are a major cause
for morbidity (by reducing autonomy and quality of life) and mortality.
Brain metastases are most common in melanoma, lung cancer, breast cancer and kidney
cancer. Treatment approaches include neurosurgical interventions, various approaches of
radiotherapy, and systemic pharmacotherapy.
Surgery and radiotherapy have traditionally been the mainstay of treatment of brain
metastasis. Stereotactic radiosurgery, often referred to as SRS and defined as a single
fraction, or stereotactic radiotherapy (SRT, consisting of several fractions), now assumes a
much more prominent role than whole brain radiotherapy for patients with brain metastasis.
SRS alone has less acute and long-term side effects and notably causes less neurocognitive
decline, compared to SRS given in combination with whole brain radiotherapy. SRS alone
might be characterised by an improved therapeutic risk benefit ratio compared with whole
brain radiotherapy, also for patients with a larger number of brain metastases.
Encouraging response rates and reasonable response duration in patients with
asymptomatic or oligo-symptomatic brain metastasis with low CNS burden treated with novel
systemic therapies including immune-checkpoint inhibitors and targeted therapy have been
reported in several cohorts of melanoma and non-small cell lung cancer (NSCLC).
With the increasing use of systemic immune-checkpoint inhibitor treatment or targeted
therapy and their induction of durable responses, the question has been raised whether
patients with brain metastases who are started on these treatments need

additional
immediate radiotherapy or whether radiotherapy can be safely delayed, without compromising brain control and overall outcome. Thus, one of the major current controversies centres on the optimal timing of SRS for patients with brain metastasis: should
it be administered upfront to optimise local control and thereby prevent neurological deficits,
with a risk of neurotoxicity in long-term surviving patients, or should radiotherapy be delayed
until systemic therapy has failed, to avoid overtreatment in patients with good response to
systemic therapy? The latter approach is increasingly preferred by medical oncologists,
based e.g. on response rates with immune-checkpoint inhibition in the range of 46-55% in
melanoma and of 30% in NSCLC with PD-L1 expression in tumour cells of more than 1% and with targeted therapy of up to 60% in melanoma (BRAF-mutant) and up to 88% (gefitinib) in epidermal growth factor receptor (EGFR) mutant NSCLC, albeit in
selected patient groups. Yet, the best approach remains controversial because there are
concerns that at least a minority of patients may no longer be eligible for SRS and may have fixed neurological deficits at the time of further progression. Additionally, responses to systemic therapies are often limited in time and a delay of radiotherapy therefore requires
frequent cranial MRI follow-up. Thus, a systematic meta-analysis of mostly uncontrolled data
suggests improved overall survival after early combination of immune-checkpoint inhibitors
and SRS compared to a sequential approach.

Study objective

The primary objective of the study is to assess the efficacy in terms of CNS-specific PFS of
the combination of standard systemic treatment plus SRS versus standard systemic treatment alone in patients with newly diagnosed and untreated (except for surgery)
asymptomatic or oligo-symptomatic brain metastases from melanoma or non-small cell lung
cancer, with indication for systemic therapy.

Secondary objectives:
- To evaluate secondary measures of clinical efficacy, including OS, CNS-response
rate, duration of CNS-response, pattern of CNS-progression and extra-CNS PFS
- To assess the safety and tolerability of SRS in combination with standard

systemic
treatment
- To evaluate changes in neurocognitive function
- To evaluate changes in quality of life and functional independence
- To assess the above measures of efficacy and safety in the overall study population and within each tumour cohort

Study design

Prospective phase III, multicentre randomised (1:1) open label superiority study

Intervention

The treatment regimen within the ETOP 19-21 USZ-STRIKE study consists of standard
systemic treatment with (Arm A) or without (Arm B) stereotactic radiosurgery.

Study burden and risks

Radiotherapy may cause side effects that include:
- Fatigue
- Seizures
- Hair loss
- Worsening of neurological symptoms such as headache, sensory problems (vision, hearing, taste) or motor disturbances (coordination, balance)
- Worsening of mental functions (worsening of attention, memory or language).

A blood sample for laboratory tests can cause bruising at or near where the needle
enters the vein and can increase the risk of infection.
For radiological tests requiring injection of contrast dye, there is a risk of an allergic
reaction.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Newly diagnosed, previously untreated (except for surgery, see below) asymptomatic or oligo-symptomatic brain metastases, e.g., controlled symptomatic seizure disorder. Note: patients with neurological symptoms or signs that require more than a stable dose of 4 mg dexamethasone equivalent for more than one week are not considered oligo-symptomatic.
2. Requirements for brain metastases:
- Brain metastases must be previously untreated, except for surgery.
- Prior surgery (including biopsies, resection, and cyst aspiration) for brain metastases is allowed. Residual and measurable disease after surgery is not required, but surgery must have confirmed the diagnosis. An MRI performed within 72 hours post-surgery should be available.
- Number and size of metastases at diagnosis of brain metastases:
° Maximum 1-10 brain metastases
° At least one brain metastasis must be of >=5 mm in diameter
° In case of 1-4 brain metastases:
- Longest diameter of largest brain metastasis must be <=30 mm
° In case of 5-10 brain metastases:
- Largest metastasis must be <=10 mL in volume and longest diameter must be <=30 mm
- Maximum cumulative brain metastases volume must be <=30 mL
3. Primary disease of histologically confirmed (from primary tumour or from a metastatic lesion, including in the brain) melanoma or NSCLC.

4. Requirements for patients with melanoma:
- Prior treatment, including treatment with immune-checkpoint inhibitors is permitted, but brain metastases must be newly diagnosed and previously untreated (except for surgery).
- BRAF-mutation status, locally assessed, should be known previous BRAF-targeted therapy is allowed).
5. Requirements for patients with NSCLC:
- Newly diagnosed, treatment-naïve (except for prior surgery) metastatic NSCLC, with or without a targetable oncogenic driver alteration: sensitising EGFRmutation (exon 19-del and 21-L858R), ALK- or ROS1-fusion.
- Known PD-L1 expression status (from primary tumour or from a metastatic lesion, including brain)
- Known driver mutation status (from primary tumour or from a metastatic lesion, including brain).
6. Age of 18 years or older
7. Karnofsky performance status of 60 or more
8. Life expectancy >12 weeks
9. Patients must be candidates for systemic treatment, within one of the following treatment cohorts planned:
- Immune-checkpoint inhibition therapy for patients with metastatic melanoma with or without BRAF-mutation. Either: the combination of ipilimumab plus nivolumab or anti-PD-1/L1 monotherapy
- Targeted therapy for metastatic NSCLC with targetable oncogenic driver mutation (EGFR-mutation or ALK- or ROS1-fusion)
- Immune-checkpoint inhibition (including an anti-PD-1/L1 compound) alone or in combination with chemotherapy for metastatic NSCLC without a targetable oncogenic driver alteration.
10. Women of childbearing potential, including women who had their last menstruation in the last 2 years, must have a negative urinary or serum pregnancy test within 7 days before randomisation.
11. Written IC for study participation must be signed and dated by the patient and the investigator prior to any study-related intervention.

Exclusion criteria

1. Confirmed or probable leptomeningeal metastasis according to EANO ESMO criteria.
2. Symptomatic brain metastases at time of randomisation, e.g., neurological symptoms or signs that require more than a stable dose of 4 mg dexamethasone equivalent for more than one week.
- Patients must be off steroids or on a stable dose of <=4 mg dexamethasone equivalent for one week prior to randomisation.
- Patients experiencing seizures controlled by anti-epileptic drugs are eligible.
3. Prior whole brain irradiation or focal radiation therapy to the brain

4. Prior systemic treatment for brain metastases
5. Contra-indication for SRS
6. Judgment by the investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and
requirements.
7. Women who are pregnant or in the period of lactation.
8. Sexually active men and women of childbearing potential who are not willing to use an effective contraceptive method during the study.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	05-09-2024
Enrollment:	25
Type:	Actual

Medical products/devices used

Registration:	No

Ethics review

Approved WMO

Date:	23-05-2023
Application type:	First submission
Review commission:	METC NedMec

Approved WMO Date:	10-04-2024
Application type:	Amendment
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT05522660
CCMO	NL82181.041.22